Profile

Susan Greenfield: from maverick scientist to media darling

Georgina Ferry

"I never say no to anything," says the neuroscientist Susan Greenfield, "without giving myself time to think about it." This openness to new possibilities perhaps goes some way towards explaining how someone who left school with no qualifications in science is now Britain's foremost scientific celebrity. Winner of this year's Faraday Award, given by the Royal Society to the scientist who has done most to further the public understanding of science in the UK, she has also just taken up the post of Director of the Royal Institution (RI). This 200-year-old scientific society holds regular events for members and the general public at its imposing establishment in the heart of London's West End. Greenfield's appointment indicates a desire on the part of the RI to widen its appeal to members and non-members alike.

The RI pioneered efforts to increase the public's understanding of science through its Christmas Lectures, inaugurated by Michael Faraday in 1826. Greenfield shot to public notice when, as a lecturer in the pharmacology department at Oxford University, she became the first woman ever to give the lectures, which are televised by the BBC. The lecture series, *Journey to the Centres of the Brain*, started a trickle of requests for media appearances. Journalists and producers quickly discovered that Greenfield was a personable and engaging speaker, who could be relied on for a soundbite on anything from young people and drugs to the nature of human consciousness.

The trickle became a torrent. Radio and television chat shows, magazine interviews, public lectures, a fortnightly column in the *Independent on Sunday* ("it allows me to exercise my bigotry on any topic"), and a succession of popular books has meant that she is rarely out of the public eye. This autumn she will present a four-part series on drugs, for national radio, and next year she will present six one-hour programmes on the brain for BBC television.

Greenfield has found the experience hugely enjoyable. "Scientific papers have to be written in a very rigid format," she says. "Writing for the press is very different: I enjoy thinking up an arresting image, using a freer form of expression, whether I'm sounding off about science policy, or talking about the brain." Commentators such as Bernard Dixon have applauded the willingness of Greenfield and others to participate not only in the dissemination of science but "its reintegration into the intellectual life of our times" (*Curr Biol* 1997, **7:**R396). But such activities continue to raise eyebrows among the majority of scientists, who cultivate a fastidious horror of anything that smacks of self-promotion.

Greenfield, however, has never been afraid to seem unconventional. She did A-levels (High School exams) in mathematics, Latin, Greek and ancient history, then went to Oxford to do a Bachelor's degree in experimental psychology. Realising that she was more interested in the nuts and bolts of brain function, she accepted her tutor's challenge that she try research, and despite a lack of lab experience was accepted as a doctoral student by David Smith in the Pharmacology Department at Oxford, in the 1970s.

After postdoctoral positions in Paris and New York, she returned to Oxford and established a lab exploring the non-cholinergic release of cholinesterase from neurons. She found that neurons in the substantia nigra — the brain region that is destroyed in Parkinson's disease — release cholinesterase from their

Susan Greenfield: at home in the public eye

dendrites in a manner that is not related to levels of its normal substrate, acetylcholine. She has suggested that cholinesterase has a neuromodulatory role, which could have implications for the treatment of Parkinson's disease and other degenerative diseases such as Alzheimer's and motor neuron disease.

Her findings were initially greeted with some scepticism. Greenfield freely admits that it is not the sort of work that readily attracts funding from the usual public sector sources, and for much of the past decade she has been one of the beneficiaries of the £10 million in research grants that Bristol–Myers Squibb awarded the Pharmacology Department in 1987. Today she feels the work is gradually gaining acceptance, as others investigate the same phenomenon.

In 1997 she felt sufficiently confident to launch a company, Synaptica, to take forward the commercial development of a peptide that she and a colleague, David Vaux, have identified as the key part of the cholinesterase molecule. The 15 researchers in her lab are now almost all supported from the funds raised privately to launch the company, in which Oxford University is the largest single shareholder.

How Greenfield came to accept the RI job gives a whole new meaning to the expression 'having it

all'. "My immediate worry was that as Director I would have to give up research, which has always been my biggest excitement," she says. But she worked out a deal with the RI and Oxford University which allows her to keep her lab in Oxford for up to four years — time enough to establish whether or not Synaptica will take off on its own. Unlike previous Directors, she will not supervise the research work of the RI's own Davy–Faraday Laboratory. She will concentrate on raising the public profile of the RI, establishing it as a centre for thinking about science, while at the same time trying to reach a wider audience. And she will still make the television series, which commits her to 120 days of filming.

"You have to remember that I always get up at 5.00am and work a 12-hour day," she says. "It's true that I do very little at the bench, but the important thing is the quality of the time, not the quantity. I often think that doing so many outside things has meant that I use my time more efficiently."

If Synaptica fails, Greenfield is sanguine about the possibility that she may have burnt her boats as a research scientist. "I can envisage the possibility of focusing on my more theoretical writing on topics such as consciousness," she says. "I could not go back to publicly-funded, i-dotting, t-crossing work. I may not qualify by the usual criteria as a successful mainstream scientist, but I'm very happy being myself." She has learned to live with colleagues who, while rarely criticising her to her face, show their disdain — or jealousy? — by avoiding any reference to her success on the public stage. "If the situation was reversed I'd probably do the same," says Greenfield frankly. "It's just human nature. This sort of pursuit is not for people who worry about that kind of thing."

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Essay

A manifesto for microbial genomics

Carl R. Woese

The future of biology lies in genomics. As the current titanic struggle over the Human Genome Project attests, the knowledge and power inherent in genomics are staggering. Frankly, I don't know whether all this hubbub will ultimately work to the benefit or detriment of the Human Genome Project. But I don't really care, for it is clear to me that in the long run the sequence of the human genome — despite its vast medical potential — will not, in itself, make a major contribution to our understanding of biology.

The Human Genome Project is distorting our view of genome sequencing

What does concern me about the Human Genome Project, however, is the way in which it is distorting our view of genome sequencing, tending to inhibit the sequencing of other important genomes, mask the deeper, more general, reasons for genome sequencing and suppress an approach to genome sequencing that would otherwise benefit a wider spectrum of biologists.

DNA sequencing initially followed a natural progression. With improving techniques, the amount of data generated per year steadily increased, more or less at an exponential pace, and the sizes of the pieces of DNA sequenced increased proportionately. Interest in the budding field grew as the small viral genomes were sequenced. By the time the human genome started to attract attention, large viral genomes were being sequenced and the next logical step in the progression would have been the sequencing of small bacterial ones.

I remember a conversation I had with Sydney Brenner in 1982 — on the occasion of the Darwin Centenary in Cambridge, UK — in which he casually said that he was considering sequencing a third of a *Rhodobacter* genome, that is, about two million base pairs of DNA. I was stunned that nucleic acid sequencing had progressed so far, so fast. The day of bacterial genomics had arrived — and just in time. The archaebacteria (as the group was then called) had been discovered only five years before, and their characterization lagged decades behind that of the eubacteria. Something drastic like genome sequencing would be needed to bring the Archaea up to speed and I returned to the University of Illinois with a single purpose: to set up a microbial genome sequencing project.

But in the mid-1980s the Human Genome Project came onto the scene and began to dominate it. Those driving the project — and many other people — saw the human genome as the ultimate goal towards which all genome sequencing was directed, and there was no need to delay further by ramping up through the microbial genomes of various sizes. The major effort should go into developing the methodology to sequence the human genome — which was about three orders of magnitude too large for technology to handle at that stage — and to sequence the genomes of a few 'model organisms' that would be useful in interpreting it. This, effectively, spelled the end for any fledgling microbial genome sequencing projects.

Microbial genomics began to re-emerge, however, in the mid-1990s, thanks in large measure to the microbial genome program instituted by the US Department of Energy, which served to break the conceptual

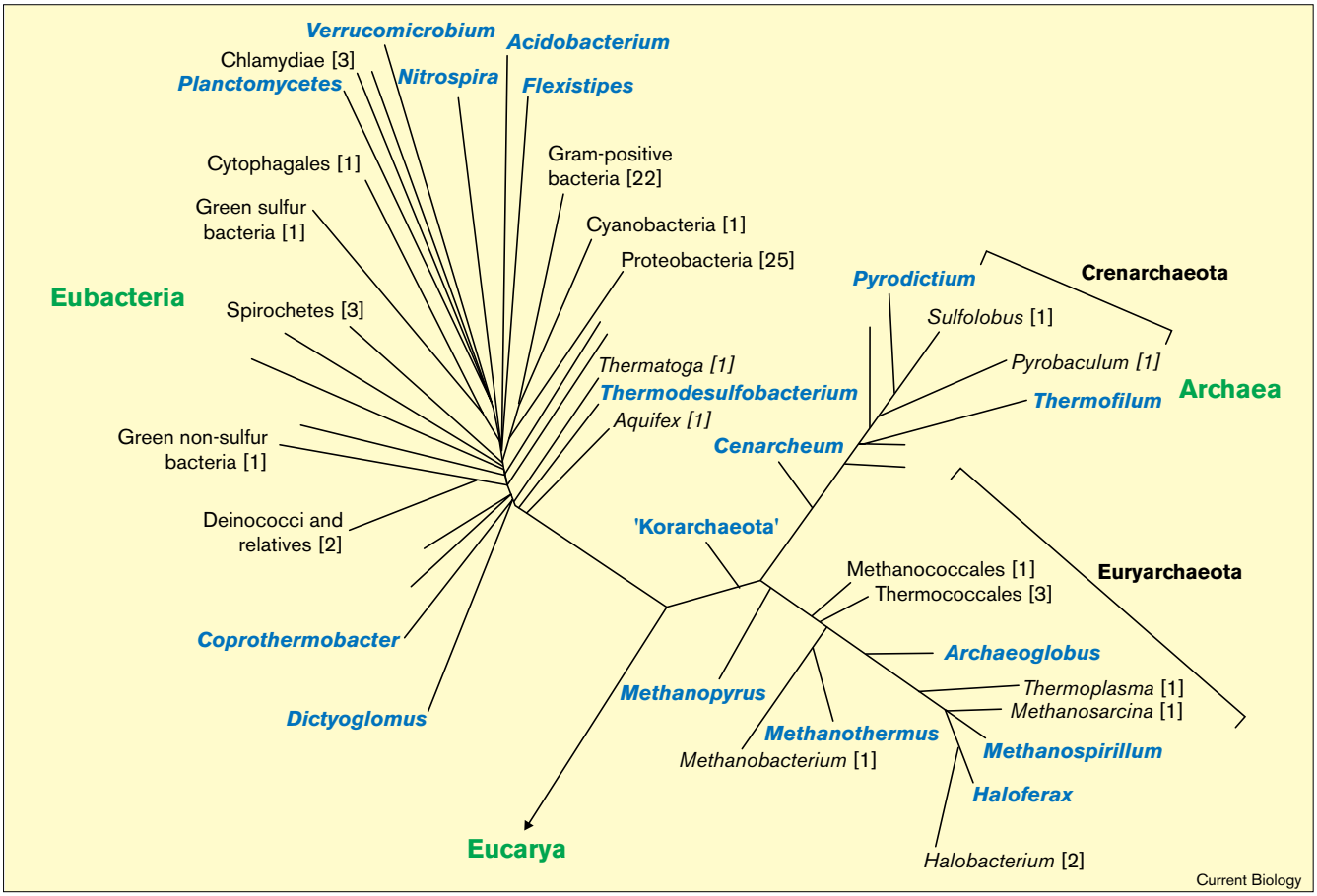
ice, as it were. The feasibility of, and ease with which, microbial genomes could be sequenced was strikingly demonstrated in 1995 when The Institute for Genomic Research published the complete sequence of the *Haemophilus influenzae* genome.

In arriving late, microbial genomics did not arrive *tabula rasa* (as it would have, had nucleic acid sequencing progressed according to the old paradigm). The Human Genome Project had set the tone for all genomics. And such a climate was, at best, alien for microbial genomics. Because the human genome had been rationalized to science and society in terms of its medical benefits, from the start microbial genomes were rationalized similarly, each for a different specific practical purpose: medical, agricultural, industrial, bioremedial, and so on.

Although goals of this sort are laudable, and of benefit to microbial genomics in the short run, it is the future reasons for selecting microbial genomes for sequencing that concern me. Microbial genomics is potentially a far richer, deeper discipline than rationalizations such as these would suggest. Rationales for sequencing microbial genomes need to come from within the discipline, not from outside it.

Given the suddenness with which the Human Genome Project burst on the scene and the hegemony it exerts over the field, microbiologists did not have the time or the freedom to develop an appropriate, overarching concept for microbial genomics. And now that microbial genome

Figure 1



Unrooted phylogenetic tree depicting the archaeal and eubacterial domains of life. Figures in brackets indicate the number of genomes that are either sequenced completely or for which sequencing is currently in progress in a given taxon. Taxa labelled in blue are not represented by any genome sequence. Of the more than 30 major bacterial taxa now known, more than 20 are not represented by any genome sequence. Branches without labels represent environmental rRNA sequences for which there are no cultivated organisms. The Archaea are divided into three kingdoms: Euryarchaeota, Crenarchaeota and 'Korarchaeota'.
Information is summarized at the following web sites: The Institute of Genome Research at http://www.tigr.org/tdb/mdb/mdb.html; http://www-c.mcs.anl.gov/home/gaasterl/genomes. (Figure adapted from originals by: Raju Aravalli, Institute of Molecular Biology, University of Copenhagen, 1307 Copenhagen, Denmark; Kirk Harris, Department of Plant and Microbial Biology, University of California, Berkeley, California 94720–3102, USA.)

sequencing is under way, it would seem that many do not feel a need to develop one. But the need is not only there, it is critical.

I say all this for one simple reason: all life turns on microbial life. The biosphere is largely defined by, and completely dependent on, the metabolism of, and interactions among, microorganisms. The study of microorganisms is important not because of the diseases they produce; to study microbiology is to study the biosphere. The primary purpose of microbial genomics has to be a global understanding of the microbial world.

Because mankind is stressing the biosphere, there will soon come a day when a deep knowledge of the biosphere and its capacity to adapt will be critical. Herein lies the ultimate justification for microbial genomics and, I believe, the ultimate justification for genomics in general.

Microbial genomics has two main goals: to explore and understand microbial diversity (the term used here to include the interactions among microorganisms and with their environments); and to lay bare the 'evolutionary dynamic' (the interplay between genes that are evolved and inherited within a given lineage and genes that have been acquired from other lineages, the nature of major evolutionary jumps, and so on).

The first order of business in microbial genomics should be a phylogenetically representative genomic screen of the microbial world. In other words, all the major microbial taxa and their subdivisions — which are the major source of biological diversity on Earth — should be represented by several genome sequences. There are now more than 30 recognized major eubacterial taxa — each the phylogenetic equivalent of a eukaryotic kingdom — and at least half that number in the (far less well characterized) Archaea; not to mention the yet-to-be-discovered kingdoms among the unicellular eukaryotes.

The fact that there are now more than 60 eubacterial genomes in the genome sequencing queue (and about 10 of them done) might suggest that we are well on our way to accomplishing this goal. But look again. All of these have been chosen for individual and 'practical' reasons. And so, their phylogenetic distribution is far from representative (see Figure 1). The relatively poor representation of archaeal genomes and the pathetic representation of the genomes of lower eukaryotes in this list underscores the point. It is essential that, in the first instance, phylogenetic considerations dictate the choice of genomes. Rest assured, however, that all manner of practical benefits would also flow naturally from the kind of concerted program I have in mind for microbial genomics — and in some cases they would come about sooner rather than later because of the solid conceptual framework that develops around an approach of this type.

The second order of business (second only because it is dependent on the first) is to sequence those genomes of value in elucidating the evolutionary dynamic. The adaptive nature of our biosphere is a study in 'horizontal gene transfer' (the transfer of genes from one genetic lineage to another). Major evolutionary jumps (what evolutionists call macroevolution) are associated with major changes in the global environment. We do not understand these events and we certainly do not want to tip global balances.

The above is a vague sketch of a five-year plan for microbial genomics — that is all the time that would be needed to make microbial genomics a mature field of study. The object is to generate as much useful information as possible, as quickly and as inexpensively as possible. Using a shotgun sequencing approach, it is reasonable to expect that a fairly complete picture of at least 200 microbial genomes could be generated within two years and that the sequences could be refined and the number of genomes also extended in the remaining three years. The cost of this would be rather less than that of the human genome and, given the amount of useful information generated, reasonable by the standards of microbiology. The genomic information would change our perception of microorganisms, of microbiology, of the biosphere and of biology itself. Although such a program is feasible, it will be undertaken only if biologists appreciate its value.

This is not the place to go into the specifics of which microbial genomes would be most useful. I would suggest, however, that a phylogenetic tree hang on the wall of every laboratory in which microbial genomes are being sequenced — for inspiration.

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